REMARKS

Introductory Remarks

Claims 35-39, 46 and 47 are pending in this application.

THE REJECTIONS

35 U.S.C. § 103(a)

Claims 35-39, 46 and 47 stand rejected under 35 U.S.C. §103(a) as "unpatentable" over Ramshaw et al., *Trends Immunology Today* 21, pp. 164-165 (2000) ("Ramshaw") and Haglund et al., *J. Virol.* 76, pp. 2730-2738 (2002) ("Haglund"), in view of Haglund et al., *J. Virol.* 76, pp. 7506-7507 (2002) ("Haglund$_b$") and Gherardi et al., *J. Virol.* 74, pp. 6278-6286 (2000) ("Gherardi"). The Examiner concedes that Ramshaw does not teach a DNA plasmid prime with a VSV vector boost as claimed. According to the Examiner, Ramshaw teaches a vaccine using a DNA plasmid prime and a poxvirus vector boost, Haglund and Haglund$_b$ teach the use of VSV vectors for the prime and the boost with an immune response that was higher than with a vaccinia virus vector indicating VSV is a preferred over vaccinia virus vectors for vaccines, that Haglund$_b$ additionally teaches the prior art use of DNA plasmid/viral vector prime/boost vaccines and that Gherardi teaches the use of IL-12 with a DNA plasmid/vaccinia virus vector boost. Applicants traverse.

The Examiner Has Not Taken Into Account the True State and Breadth of the Art at the Time Applicants' Claimed Invention Was Made

Applicants respectfully submit that the Examiner has not taken into account the true state and breadth of the art at the time Applicants' claimed invention was made. Instead, the Examiner has relied on a narrow selection of art prompted by impermissible hindsight.

- There was an array of immunization approaches available at the time Applicants' invention was made.

- There was an array of combinations of immunization approaches available at the time Applicants' invention was made.

- There was no guidance in the art cited by the Examiner to direct the person of ordinary skill in the art to Applicants' claimed invention.

Many alternative systems were developed for presentation and/or delivery of immunogens (this listing is not exhaustive):

A – protein/polypeptide
B – plasmid DNA
C – adenovirus vector
D – adeno-associated virus vector
E – alphavirus vector such as Venezuelan equine encephalitis virus (VEE) and Semliki Forest virus
F – flavivirus vector such as dengue
G – herpes simplex virus vector
H – Lactobacillus vector
I – Paramyxovirus vector such as Sendai virus
J – poliovirus vector
K – poxvirus vector such as MVA
L – proviral DNA
M – Salmonella vector
N – Vesicular stomatitis virus vector

Many of these systems have been used in combination, see the following non-limiting examples:

B + K
B + A
B + C
B + G

E + K

L + I

M + K

Many additional combinations are possible from the list of A through N above.

The Examiner's argument may be reduced to the following: combining B + K (Ramshaw) with M + K (Haglund$_b$) yields Applicants' claimed B + M. The hindsight nature of this argument is abundantly clear. The Examiner cannot arbitrarily select only a small subset of possible approaches and then combine that subset without any suggestion to do so.

The Examiner's argument also flies in the face of the unpredictability of combinations, as shown by the negative results seen with other prime-boost regimens. Even the combination used by Ramshaw did not provide boostable antibody responses, and, as discussed below, Allen et al., Horton et al. and Woodberry et al. all had negative results using Ramshaw's combination.

Ramshaw, the Examiner's Primary Reference, Failed to Produce Boostable Antibody Responses

Two types of immune response are needed for an efficacious immunogenic composition: (1) An antibody response, and (2) a cell-mediated immune response. Ramshaw et al. ("Ramshaw"), the primary reference cited by the Examiner, was unable to provide a boostable antibody response, and the Haglund and Haglund$_b$ secondary references cited do not cure this deficiency.

Ramshaw at page 164, left column, stated:

"Interestingly, only low levels of specific antibodies were raised following DNA vaccination, and these declined markedly following FPV [fowlpox virus] boosting, despite a marked Th-cell proliferative response against both encoded HIV proteins, indicating a strongly biased Th1-type immune response."

These data were reported in reference 10 to Ramshaw. Reference 10 is Kent et al., *J. Virol.* 72, pp. 10180-10188 (1998), in which Ramshaw was the senior author (a copy of Kent et al. is being provided with Applicants' accompanying Supplemental Information Disclosure Statement). Thus, Ramshaw's own data indicated that his plasmid DNA/FPV regimen was unable to boost an already low antibody response.

This is in sharp contrast to Applicants' plasmid DNA prime/VSV boost regimen. Figure 4 of the instant application demonstrates that antibodies were raised in non-human primates in a statistically significant manner over those raised in animals receiving multiple doses of plasmid DNA alone or VSV alone.

Ramshaw contends that a replication-defective virus is desirable because it does not integrate into the recipient's genome (page 163, left column). Plasmid DNA is replication-incompetent, and fowlpox and MVA as used by Ramshaw were replication-incompetent. However, VSV can be either replication-incompetent (Applicants' claim 37) or replication-competent (Applicants' claim 36).

Ramshaw also stated at page 164, right column that the nature of the boosting virus is important for effective prime-boost immunization. Merely "changing the strain of VV [vaccinia virus] from MVA or the closely related NYVAC strain to the WR strain (which replicates extensively in mice) resulted in a failure of protection." (Emphasis added.) Thus Ramshaw recognized the unpredictable nature of the selection of the boosting virus, even when merely switching from one vaccinia virus to another vaccinia virus. Applicants respectfully submit that the unpredictability would be even higher in switching from vaccinia virus (a positive sense, double stranded DNA poxvirus) to the taxonomically distant VSV (a non-segmented, negative sense, single stranded RNA rhabdovirus). The only way to establish the efficacy of a given boosting virus, and indeed of a prime-boost combination, is by extensive experimentation.

Haglund and Haglund$_b$, the Examiner's Secondary References, Contradict the Purported Teachings of Ramshaw

Furthermore, the Examiner's secondary references, Haglund and Haglund$_b$, directly and unambiguously contradict the purported teachings of Ramshaw. Ramshaw indicated that low level focused priming is desirable in order to achieve a good boost.

In contrast, Haglund used replication-competent VSV only to express HIV gag as a primary immunogen (and did not use a prime-boost regimen) and obtained a response 8-fold higher than vaccinia virus expressing gag.

Haglund and Haglund$_b$ are both silent on the best combination for eliciting an antibody response.

Also in contrast, Haglund$_b$ tested the following regimens:

- Homologous VSV/VSV prime-boost;
- Heterologous VSV prime-vaccinia boost (where the VSV elicited a high-level memory response which was amplified 6-8 fold by the vaccinia boost); and
- Heterologous vaccinia prime-VSV boost (response was reduced 25-30% compared to VSV prime-vaccinia boost).

Haglund$_b$ indicates that the level of priming response predicts the level of memory response achieved by boosting. This is inconsistent with the observation by Ramshaw that low level focused priming is desirable in order to achieve a good boost.

Because Haglund$_b$ is inconsistent with Ramshaw, this makes it improper to combine them, as the Examiner has sought to do.

If Haglund$_b$ and Ramshaw teach anything, it is that the magnitude and the quality of the immune response are both important. Given the unpredictability of their results, as well as the results of the other publications discussed below, it is not obvious that any particular prime-boost combination will achieve both the desired magnitude and quality of the immune response.

Only Applicants' claimed combination resulted in a profound boosting of the antibody response and the cell-mediated immune response. None of the references cited by the Examiner achieved this; each had a deficiency in at least one of these two responses.

Unlike the Examiner's Cited References, Applicants' Claimed Combination Resulted in a Profound Boosting of Both the Antibody Response and the Cell-Mediated Immune Response

Unlike Ramshaw's plasmid DNA prime-MVA boost combination or Haglund$_b$'s VSV prime-vaccinia boost combination, Applicants' claimed plasmid DNA prime-VSV boost combination elicits both antibody (Figure 4) and cell-mediated immune (Figure 5) responses that are statistically significant and more than additive.

As paragraphs 2-7 of Applicants' specification make clear, Applicants were not the first to devise a generic concept of priming with plasmid DNA, followed by boosting with a protein or a recombinant virus vectoring a gene of interest. However, these same paragraphs summarize some of the problems with these other prime/boost regimens.

Paragraph 24 of Applicants' specification describes the unexpected result of an increased $CD8^+$ T-cell response that was more than merely additive.

Paragraph 104 of Applicants' specification describes the achievement of a humoral (antibody) response, which is in addition to the cell-mediated response discussed above.

Example 3 of Applicants' specification describes in detail the results of the prime-boost immunization regimen in rhesus macaques. The results are depicted in Figures 2-5 and Table 1. Paragraph 151 summarizes the unexpected results as follows:

"The results of these assays demonstrate a surprising synergistic effect of a prime/boost regimen according to this invention, when compared to the results of administering multiple priming compositions only and multiple boosting compositions only. The combination of the presentation of the desired antigen by a DNA plasmid administration followed by an rVSV boost

produces an increase in antigen-specific T cells in the immunized subject, which is considerably in excess of any additive response. Similarly, the increase demonstrated in the humoral response to the desired antigen is unexpectedly high with the use of both the DNA plasmid and rVSV immunogenic compositions in an immunization protocol."

These unpredictable results are evidence of nonobviousness.

Others Using DNA Prime/Poxvirus Boost Reported Negative Results – This Contradicts Ramshaw

Even Ramshaw, the Examiner's primary reference, is contradicted by other contemporaneous scientific literature. This is exemplary of the unpredictable results described in the contemporaneous scientific literature.

In a paper published two years after Ramshaw, it was shown that a DNA prime-MVA boost vaccine regimen encoding HIV tat was unpredictable and unsuccessful. See, e.g., Allen et al., *J. Virol.* 76, pp. 4108-4112 (2002). In the Abstract at page 4108, it is stated:

"The regulatory proteins of human immunodeficiency virus may represent important vaccine targets. Here we assessed the role of Tat-specific cytotoxic T lymphocytes (CTL) in controlling pathogenic simian immunodeficiency virus SIVmac 239 replication after using a DNA-prime, vaccinia virus Ankara-boost vaccine regimen. Despite the induction of Tat-specific CTL, there was no significant reduction in either peak or viral set point compared to that of controls." (Emphasis added.)

See also the statement at page 4109, right column of Allen et al.:

"However, by week 10 [post SIV challenge], viral loads in the vaccinees and controls were indistinguishable ($p = 0.954$; t = test 1)(Fig. 3)."

The supposed teachings of the Examiner's primary reference, Ramshaw et al., are contradicted by another study using the exact same DNA prime/MVA boost regimen. See Horton et al., *J. Virol.* 76, pp. 7187-7202 (2002). The second half of the Abstract is worth quoting in its entirety:

"In this study, we used a DNA prime/modified vaccinia virus Ankara boost regimen to immunize rhesus macaques against nearly all simian immunodeficiency virus (SIV) proteins. These animals were challenged intrarectally with pathogenic molecularly cloned SIVmac239, which is resistant to neutralization. The immunization regimen resulted in the induction of virus-specific $CD8^+$ and $CD4^+$responses in all vaccinees. Although anamnestic neutralizing antibody responses against laboratory-adapted SIVmac251 developed after the challenge, no neutralizing antibodies against SIVmac239 were detectable. Vaccinated animals had significantly reduced peak viremia compared with controls ($P < 0.01$). However, despite the induction of virus-specific cellular immune responses and reduced peak viral loads, most animals still suffered from gradual CD4 depletion and progressed to disease." (Emphasis added.)

See also page 7188, left column. More detailed results are presented at page 7196:

"However, by 12 weeks postinfection, the viral loads in all vaccinees increased to levels comparable to those in the controls." (Left column)

"There was also no correlation between either the strength or the breadth of the virus-specific $CD8^+$ responses detected in each animal and its ability to maintain CD4 counts." (Right column)

In the Discussion at page 7197, right column, it is stated:

"These results are somewhat disappointing, since recent studies with similar DNA prime/viral vector boost approaches protected rhesus macaques from the pathogenic consequences of infection with SHIV-89.6P (9,80)." (Emphasis added.)

Reference 9 is listed in the References on page 7199 and its title is: "Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine". Reference 80's title is: "Neutralizing antibody-independent containment of immunodeficiency virus challenges by DNA priming and recombinant pox virus booster immunizations".

Finally, at page 7198, right column, Horton et al. stated:

"The failure of our immunization strategy could be due to several factors." (Emphasis added.)

Thus, Horton et al. reported that the same DNA/poxvirus regimen as that used in references 9 and 80 – as well as in Ramshaw – was not successful. This result casts doubt about the value of the supposed teachings of the Ramshaw reference.

Another paper which contradicts Ramshaw is Woodberry et al., *J. Immunol.* 170, pp. 2599-2604 (2003). Woodberry also used a DNA prime/MVA boost regimen. At page 2601, left column, Woodberry reported:

"Importantly, DNA prime and MVA boost immunizations did not appear to provide better protection for the number of CD8 T cells than any other vaccination strategy (Fig. 3, combinations 7 and 8). Thus, these data do not support the notion that DNA prime and MVA boost immunizations induce CD8 T cells with superior IFN-γ-independent protective capabilities."

Specifically, Woodberry went on to contrast his findings with those of Ramshaw at page 2603, right column:

"However, perhaps the most surprising outcome is the observation that the number of CD8 T cells induced following prime boost immunizations approximates to the simple addition of the responses seen when the prime and boost vaccination modalities were administered individually. This $1 + 1 \approx 2$ concept contrasts with Ab [antibody] responses following prime boost

immunizations where substantial synergistic affects are obtained (7)[this reference is Ramshaw]."

These three articles contradict Ramshaw and demonstrate that the results of a DNA prime/poxvirus boost regimen are unpredictable.

Many Individual Immunization Regimens Were Known

As of the March 26, 2003 filing date of Applicants' first priority provisional application number 60/457,876, the person of ordinary skill in the art had a very large number of individual immunization regimens from which to choose. A non-comprehensive, non-limiting listing of such regimens includes the following:

A. Protein/Polypeptide

Protein-based vaccines have been use for a number of years. One example is the Hepatitis B vaccine which utilizes the recombinantly-expressed surface antigen, which was developed in accordance with Murray U.S. patent 4,710,463.

B. Plasmid DNA

Plasmid DNA has been used as a vector for vaccine antigens in a variety of formulations. See, for example, Felgner et al. U.S. patent 5,589,466, and Weiner et al. U.S. patent 5,593,972.

C. Adenovirus

Xiang et al., *J. Virol.* 76, pp. 2667-2675 (2002) reported on the utility of adenovirus as a vector for rabies virus glycoprotein. See Abstract:

"An E1-deletion-containing adenoviral recombinant based on the chimpanzee serotype 68 (AdC68) was developed to express the rabies virus glycoprotein. Mice immunized with this

construct (AdC68rab.gp) developed antibodies to rabies virus and remained resistant to challenge with an otherwise lethal dose of rabies virus."

Xiang et al. stated that adenovirus was a superior vector compared to vaccinia virus or DNA (page 2667, left column):

"The immune responses to the transgene products far surpass those achieved with other types of subunit vaccines, such as vaccinia virus recombinants or DNA vaccines." (Emphasis added; citations omitted.)

D. Adeno-Associated Virus

Adeno-associated virus (which is different from adenovirus) has long been used to introduce foreign DNA into mammalian cells. See, e.g., Hermonat et al., *Proc. Natl. Acad. Sci. USA* 81, pp. 6466-6470 (1984) at Abstract and page 6466, right column.

E. Alphavirus

An alphavirus vector, Semliki Forest virus, has been used to express high levels of a stable fusion protein of human papillomavirus type 16 proteins E6 and E7; strong, long-lasting cellular immune responses were induced. See Daemen et al., *Gene Therapy* 9, pp. 85-94 (2002) at Abstract and page 85, right column.

A different alphavirus, Venezuelan equine encephalitis virus (VEE) was used as a vector for Norwalk virus-like particles by Harrington et al., *J. Virol.* 76, pp. 730-742 (2002). A positive and unexpected result was reported at page 739, right column:

"The fact that subcutaneous inoculation of VEE VRPs resulted in the production of mucosal antibody is a conundrum to conventional perception of mucosal immune induction." (Emphasis added.)

F. Flavivirus

Pang et al., *BMC Microbiology* 1, pp. 1-9 (2001), described the use of dengue virus, a flavivirus, as a vector for expressing HIV gp120 and gp160. See Abstract. The advantages of using dengue virus to vector HIV immunogens were set forth at page 2, left column:

"As a flavivirus, it replicates entirely in the cytoplasm through RNA directed RNA polymerization and is incapable of integrating into the host genome. Flavivirus replicons can replicate inside cells and achieve prolonged expression of high levels of virally encoded proteins with minimal toxicity and are unable to recombine or mutate to produce infectious HIV particles. Finally, by eliciting an immune reaction against the dengue non-structural proteins remaining in replicons, dengue virus replicons may induce a protective immunity against dengue which would not predispose vaccinated individuals to DHF. Properly administered, dengue virus replicons expressing HIV epitopes might thus serve as dual vaccines, conferring protection against dengue virus as well as HIV."

G. Herpes Simplex Virus

Another vector system is that of replication-defective herpes simplex virus (HSV) strains. See, e.g., Brockman et al., *J. Virol.* 76, pp. 3678-3687 (2002). Of interest is the following statement on page 3678, right column:

"Currently, many vector systems are being developed for use in vaccine design. In addition to HSV, other promising virus-derived vaccine systems include poxviruses, adenoviruses, alphaviruses and poliovirus-derived vectors." (Citations omitted.)

Conspicuously absent from this listing is VSV.

Brockman et al. also make the important point that each viral vector behaves differently. See the following statements at page 3685, left column:

"Prior immunity has been shown to decrease the efficacy of vaccine vector systems derived from certain other DNA viruses, such as poxviruses and adenoviruses. As a result, the use of these vaccine candidates may be limited by their inability to vaccinate immune individuals or to be readministered to a single patient.

"It is unclear why HSV behaves differently than these other viruses, and a greater understanding of the subtle differences between HSV and these other viral systems will be necessary to determine the reasons for the observed variations in vaccine efficacy in vivo."

"A second surprising result is the durability of the antibody responses induced by the HSV vector". (Emphasis added; citations omitted.)

H. Lactobacillus

Yet another vector system is Lactobacillus lactis, which was used by Gilbert et al., *Infection & Immunity* 68, pp. 3251-3260 (2000) for the expression of pneumococcal type 3 capsular polysaccharide. Antibodies were elicited "characteristic of those elicited by a classic T-cell-independent antigen".

I. Paramyxovirus

Matano et al., *J. Virol.* 75, pp. 11891-11896 (2001) (discussed in more detail below in the prime/boost regimen section) used Sendai virus, a Paramyxovirus, as a boosting immunization.

J. Poliovirus

The use of poliovirus as a vector is exemplified by Lee et al., *J. Virol.* 76, pp. 1649-1662 (2002). Lee et al. inserted a variety of foreign genes into poliovirus, including HIV structural proteins (page 1652, left column and Table 1). Stability of the insert was a function of G/C content rather than the size of the insert if below 450 base pairs (page 1654, right column).

K. Poxvirus

The use of the canarypox virus ALVAC as a vector to express HIV-1 gp120 was reported by Clements-Mann et al., *J. Infectious Diseases* 177, pp. 1230-1246 (1998). The Abstract summarized preliminary human studies in which both neutralizing antibodies and cytotoxic $CD8^+$ T cells were elicited.

L. Proviral DNA

Matano et al., *J. Virol.* 75, pp. 11891-11896 (2001)(discussed in more detail below in the prime/boost regimen section) used proviral DNA as a priming immunization.

M. Salmonella

Another approach tested was the use of Salmonella as a vector for expressing the major merozoite surface protein 1 (MSP1) of *Plasmodium falciparum*. See Qian et al., *Infection & Immunity* 70, pp. 2029-2038 (2002).

N. VSV

Applicants' specification describes the use of VSV to vector foreign genes including those encoding immunogens against viral pathogens. See published application US20070134200 at paragraphs [0042]-[0045].

Prime-Boost Regimens in Addition to DNA Prime/Poxvirus Boost (B+K)

As of the March 26, 2003 filing date of Applicants' first priority provisional application number 60/457,876, the following exemplary prime/boost regimens in addition to DNA prime/poxvirus boost (B+K) were known and were by no means limiting. Their diversity of success and failure provides further evidence that it cannot be predicted in advance whether a

particular prime/boost regimen is able to elicit both a functional antibody response and a functional cell-mediated response.

B+A. DNA/Protein

Hechard et al., *Vet. Res.* 34, pp. 119-125 (2003) reported that vaccination with DNA expressing the heat shock protein DnaK of *Chlamydophila abortus*, followed by boosting with that protein was not successful (see Abstract):

"The induced antibodies had no in vitro neutralizing properties on *C. abortus* infectivity. Moreover, the proteic boost probably failed to elicit an efficient cellular immune response since the pregnant or non-pregnant mice were not protected against the bacterial challenge." (Emphasis added.)

See also the statement at page 124, right column of Hechard et al.:

"[T]his immunization strategy failed to enhance the protective properties of the elicited antibodies and to induce an efficient cellular immune response. . . ."

B+C. DNA/Adenovirus

Initial reports of encouraging data with a DNA prime-adenovirus boost regimen were not sustained when further studies were conducted. Vinner et al., *J. Gen. Virology* 84, pp. 203-213 (2003), reported in the Abstract that when rhesus macaques were primed with plasmid DNA encoding HIV gp140 or gp150 and boosted with recombinant adenovirus type 5 encoding HIV gp120:

"Both the humoral and cellular responses were significantly improved following intramuscular boosting with the recombinant adenovirus."

However, a similar subsequent study reported "vaccine failure". See McDermott et al., *J. Virol.* 79, pp. 15556-15566 (2005). The Abstract reads as follows:

"Adenovirus 5 (Ad5) vectors show promise as human immunodeficiency virus vaccine candidates. Indian rhesus macaques vaccinated with Ad5-*gag* controlled simian-human immunodeficiency virus SHIV89.6P viral replication in the absence of Env immunogens that might elicit humoral immunity. Here we immunized 15 macaques using either a homologous Ad5-*gag*/Ad5-*gag* (Ad5/Ad5) or a heterologous DNA-*gag*/Ad5-*gag* (DNA/Ad5) prime-boost regimen and challenged them with a high dose of simian immunodeficiency virus SIVmac239. Macaques vaccinated with the DNA/Ad5 regimen experienced a brief viral load nadir of less than 10,000 viral copies per ml blood plasma that was not seen in Mamu-A*01-negative DNA/Ad5 vaccinees, Mamu-A*01-positive Ad5/Ad5 vaccinees, or vaccine-naïve controls. Interestingly, most of these animals were not durably protected from disease progression when challenged with SIVmac239. To investigate the reasons underlying this short-lived vaccine effect, we investigated breadth of the T-cell response, immunogenetic background, and viral escape from $CD8^+$ lymphocytes that recognize immunodominant T-cell epitopes. We show that these animals do not mount unusually broad cellular response, nor do they express unusual major histocompatibility complex class I alleles. Viral recrudescence occurred in four of the five Mamu-A*01-positive vaccinated macaques. However, only a single animal in this group demonstrated viral escape in the immunodominant $_{Gag181-189}$CM9 response. These results suggest that viral "breakthrough in vaccinated animals and viral escape are not inextricably linked and underscore the need for additional research into the mechanisms of vaccine failure." (Emphasis added.)

Referring to the DNA-*gag*/Ad5-*gag*-vaccinated Mamu-A*01-positive macaques, McDermott stated at page 15558, right column:

"Vaccination did not have a durable effect on viral load or survivorship . . . ."

Referring to the same animals, McDermott stated at page 15563, left column:

"However, despite an increased breadth and magnitude of IFN-γ ELISPOT responses in Mamu-A*01-positive vaccinees postimmunization, the animals ultimately failed to control virus replication following high-dose SIVmac239 challenge."

Interestingly, despite the failure of this regimen, McDermott concluded at page 15564, left column:

"In summary, the DNA prime-Ad5 boost vaccine regimen is the most immunogenic of any known vaccine strategy in the rhesus macaque model."

B+G. DNA/HSV

In contrast to Brockman's favorable results when using HSV as a vector (see above), however, when cattle were primed with plasmids encoding bovine herpesvirus-1 glycoproteins B and D, then boosted with modified live BHV-1 (MLV) vaccine, Loehr et al., *J. Gen. Virol.* 82, pp. 3035-3043 (2001), reported in their Abstract that:

"Although significantly enhanced T-cell responses were induced by priming with the DNA vaccine, there was no increase in antibody titres. Similar levels of protection were induced by the MLV vaccine alone and the DNA prime and MLV boost regimen, which suggests that there is no correlation between the induction of T-cell responses and protection from BHV-1 challenge." (Emphasis added.)

E+K. Alphavirus/Poxvirus

The Semliki Forest virus vector was used as a priming immunization for an HIV clade A antigen, followed by boosting with MVA vectoring HIV A. See Hanke et al., *J. Gen. Virol.* 84, pp. 361-368 (2003). In a single immunization regimen, Semliki Forest virus vector induced CTL responses in mice similar to those elicited by plasmid DNA, but lower compared to MVA (page 364, left column). In the DNA prime-Semliki Forest virus boost regimen, interferon gamma

ELISPOT assay results showed that that regimen was "more potent than two sequential doses" of SFV-HIV A or plasmid DNA-HIV A (page 365, left column).

M+K. Salmonella/Poxvirus

Despite the promising results with the Salmonella vector reported by Qian et al., disappointing results were reported in a prime-boost regimen of immunization of rhesus macaques with an attenuated Salmonella bacterium to vector SIV Gag protein, followed by boosting with MVA also expressing SIV gag. See Evans et al., *J. Virol.* 77, pp. 2400-2409 (2003).

Salmonella was tested by Evans et al. as a vector because, as stated at page 2406, right column:

"Despite recent advances in the development of vaccine approaches able to induce CTL responses, there is a continuing need to develop better methods to induce CTL responses able to home to mucosal sites."

Evans found that transient low-level CTL responses were detected after each dose of Salmonella, and strong Gag-specific CTL responses were consistently detected after boosting with MVA. Notwithstanding this, as stated in the Abstract:

"Yet, despite these responses, Salmonella-primed/MVA-boosted animals did not exhibit improved control of virus replication following a rectal challenge with SIVmac239."

These disappointing results are further evidence of the unpredictability of prime-boost regimens.

L+I. Proviral DNA/Paramyxovirus

Matano et al., *J. Virol.* 75, pp. 11891-11896 (2001), reported the priming with an env and nef deletion-containing SHIV proviral DNA followed by a single booster with a Gag-expressing Sendai virus which protected macaques from SHIV challenge.

From this non-comprehensive review of the literature, one conclusion is clear: It is not predictable whether any particular prime-boost combination of immunization regimens will result in boostable antibody and cell-mediated responses.

The Gherardi Reference Does Not Cure the Deficiencies of the Other References Cited by the Examiner

The Examiner states: "Gherardi's reference clearly teaches advantages of including IL-12 in the composition." Applicants respectfully state that, whatever Gherardi's teachings regarding IL-12, those teachings do not refer to a DNA prime/VSV boost regimen. Therefore, Gherardi does not cure the deficiencies of Ramshaw, Haglund and Haglund$_b$ discussed above. Therefore, Applicants' claims are not obvious over the combination of Gherardi with Ramshaw, Haglund and Haglund$_b$.

Applicants' Claimed Invention is Unobvious Under Both *KSR* and Post-*KSR* Decisions

In *KSR Int'l Co. v. Teleflex Inc.*, the Supreme Court stated:

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 550 U.S. 398, 416 (2007).

As has been documented above, the result of combining different immunization approaches in prime-boost regimens is utterly unpredictable.

The Supreme Court also stated:

"When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." 550 U.S. at 421.

Here, there were a large number of unpredictable potential solutions in a complex art, in contrast to the relatively straightforward automobile pedal design problem in *KSR*.

Several lower court cases decided after *KSR* support Applicants' position.

In *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007), the Court of Appeals for the Federal Circuit affirmed a lower court finding of validity and nonobviousness of a patent claiming certain antidiabetic compounds. The Court stated:

"Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. . . . Thus, this case fails to present the type of situation contemplated by the [Supreme] Court when it stated that an invention may be deemed obvious if it was 'obvious to try.' The evidence showed that it was not obvious to try." 83 U.S.P.Q.2d at 1176.

In another case involving antidiabetic compounds, *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 86 U.S.P.Q.2d 1196 (Fed. Cir. 2008), the Court of Appeals for the Federal Circuit affirmed a lower court finding of validity and nonobviousness of a patent, and stated:

"The record, however, shows that even if an ordinarily skilled artisan sought an FBPase inhibitor, that person would not have chosen topiramate. Moreover this invention, contrary to Mylan's characterization, does not present a finite (and small in the context of the art) number of options easily traversed to show obviousness. . . . In sum, this clearly is not the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness. *Id.* at 1742." 86 U.S.P.Q.2d at 1201.

"In other words, Mylan's expert, Dr. Anderson, simply retraced the path of the inventor with hindsight, discounted the number and complexity of the alternatives, and concluded that the invention of topiramate was obvious." 86 U.S.P.Q.2d at 1201.

In *Abbott Labs. v. Sandoz, Inc.*, 89 U.S.P.Q.2d 1161 (Fed. Cir. 2008), the Court of Appeals for the Federal Circuit affirmed a lower court finding of validity and nonobviousness of a patent claiming certain antibiotic compounds. The Court stated:

"We agree that the obviousness of selection of components, when there is no prediction in the prior art as to the results obtainable from a selected component, differs from the issue in *KSR* . . . .

"Abbott argued that the 'known options' in the prior art were not 'finite, identified, and predictable,' the words of *KSR*, and are identified only with hindsight knowledge of Abbott's new formulation and its pharmacokinetic properties. Abbott pointed to the discussion in the PCT Application of over a dozen possible drug delivery modes . . . . The expert witnesses pointed out the difficulties in predicting the behavior of any composition in any specific biological system.

. . . "Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality of the prior art, and the predictability of results in the area of interest." 89 U.S.P.Q.2d at 1170-71.

In *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008), the Court of Appeals for the Federal Circuit affirmed a lower court finding of validity and nonobviousness of a patent claiming certain proton pump inhibitor compounds. The Court stated:

"To the extent an art is unpredictable, as the chemical arts often are, *KSR*'s focus on these 'identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." 87 U.S.P.Q.2d at 1457.

The Supreme Court in *KSR* also cautioned against the use of hindsight:

"A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." 550 U.S. at 421.

In so stating, the Supreme Court followed a long line of cases in the Court of Appeals for the Federal Circuit. For example, in *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 220 U.S.P.Q. 303 (Fed. Cir. 1983), the Federal Circuit found that the Examiner has fallen "victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher." 220 U.S.P.Q. at 313. *See also Grain Processing Corp. v. Am. Maize-Prods. Co.*, 5 U.S.P.Q.2d 1788 (Fed. Cir. 1988): "Care must be taken to avoid hindsight reconstruction by using 'the patent in suit as a guide through the maze of prior art references, combining the right references in the right way so as to achieve the result of the claims in suit.' *Orthopedic Equip. Co.* v. *United States*, 217 USPQ 193, 199 (Fed. Cir. 1983)." 5 U.S.P.Q.2d at 1792.

Applicants respectfully submit that the Examiner has not demonstrated the caution against the use of hindsight which the Supreme Court in *KSR* warned against.

The holdings in these cases can be distilled down to the following: An invention is not obvious if the following factors are present:

- The number of possible alternatives is not small,
- The results obtainable from each alternative, alone or in combination, are not predictable, and
- The claimed invention is identified through the use of hindsight.

Applicants respectfully submit that each of those factors is present with respect to their claimed invention.

Therefore, under the guidance provided by the United States Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), Applicants' claimed invention is not obvious.

CONCLUSION

In view of the foregoing evidence and arguments, Applicants respectfully submit that Claims 35-39, 46 and 47 are not obvious over the art cited by the Examiner. A Notice of Allowance is respectfully requested.

Respectfully submitted,

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